REMARKS

1. General Matters

Claims 1, 4-19, 23, 24, 26-29, 36-40, 45, 46 and 48 have been amended, claims 2, 3, 20-22, 25, 32-35, 47 and 49-51 have been cancelled.

2. Definiteness Issues

2.1. The rejection of claims 21 and 22 is mooted by the cancellation of those claims.

2.2. The examiner questions the definiteness of "the enzyme exerts substantially all its enzymatic activity extracellularly in the bloodstream" (claim 24).

As noted in MPEP § 706.03(d):

> [An examiner] should allow claims which define the patentable novelty with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. [emphasis in original]

The term "substantially" is not considered indefinite per se. In In re Mattison, 184 USPQ 484 (CCPA 1975), the CCPA reversed a 112/2 rejection of a claim to a compound wherein one substituent was "so selected and positioned on the aromatic ring to substantially increase the efficiency of the compound as a copper extractant from aqueous solutions having a pH of less than about 1.0." (emphasis added). The Board had questioned whether a "substantial increase" would be "3%, 30%, 300% or something else". In upholding the claim, the CCPA declared

> We are not persuaded by the board's reasoning that one skilled in the art would not be able to determine the scope of the claimed invention in terms of a specified percentage value. General guidelines are disclosed for a proper choice of the substituent Ep together with a representative number of examples. If the prior art 2-hydroxybenzophenoxime is modified by the inclusion of an electron withdrawing substituent Ep as claimed, resulting in substantially increased efficiency of the compound as a copper extractant from aqueous solutions having a pH of less than 1.0, the

> compound is within the scope of the claims. Hypothesizing whether an increase in efficiency of 3%, 30%, or 300% is necessary for said increase to be classified as substantial is not determinative of the issue of whether the claims satisfy 35 U.S.C. 112, second paragraph. (Id. 486)

More recently, in Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ2d 2010 (Fed. Cir. 1988) the Federal Circuit remarked, in considering a claim having the phrase "substantially equal", that "the criticized words are ubiquitous in patent claims", Id., 2012. Citing Seattle Box Co. v. Industrial Crating and Packing, 221 USPQ 568, 573-4 (Fed. Cir. 1984), it held that the term "substantially equal" was acceptable "even if experimentation may be needed" to understand its scope. Id., 2013.

The Examiner's query as to whether "60%" or "99%" is enough is highly reminiscent of the rejection overruled in In re Mattison.

It is not necessary that the term "substantially" be formally defined by the specification; the standard can be inferred.

The issue is first addressed at P9, L11-18:

> Although the above embodiments are interesting, it is believed that the normal, practical embodiment of the invention will involve use of a catalyst which exerts substantially all its enzymatic activity extracellularly in the bloodstream, since it is believed that the metabolic products of the enzymatic conversion of the relevant heme precursor will permeate freely into the intracellular compartment where the remaining conversions of the heme biosynthetic pathway can take place. Alternatively, the metabolic product may be excreted from the subject via urine and/or faeces at least to some extent.

See also P13, L32-33.

The specification teaches that a reduction in enzymatic PBGD activity, results in elevated levels of delta-aminolevulinic acid (ALA) and porphobilonogen (PBG) in urine and serum. P2, L16-18. The levels are quantified at P5, L25-33. At P6, L11-16, the

specification asserts

> Hence, PBGD administered by injections will carry out its normal catalytic function by converting PBG to HMB in serum (extracellularly, not inside the cells), where it normally functions. The new therapeutic idea is based on the assumption that ALA, PBG and HMB permeate cellular membranes or are transported specifically across them. An alternative to this is to administer a form of PBGD which will be able to act intracellularly, either as a consequence of formulation or as consequence of modification of PBGD so as to facilitate its entry into cells from the extracellular compartment.

Thus, the effect of PBGD therapy provides a standard as to the meaning of "substantially all". It is respectfully submitted that with these teachings, the term "substantially", while admittedly not a specific numerical value, is sufficiently definite to comply with the patent statute.

2.3. The Examiner also questions "at least part" in claims 24 and 51. However, this phrase does not in fact appear in claim 24, and claim 51 has been cancelled.

2.4. Claims 36 and 37 have been amended to recite that the human PBGD is "encoded by", rather than "based on", SEQ ID NO:1 or 12.

2.5. Claim 25 has been cancelled because we agree with the Examiner that it does not further limit the base claim.

2.6. The rejection of claims 2, 3 and 47 is moot as those claims have been cancelled.

Claim 1 has been amended to recite both the diseases of former claim 2 and the enzymes of former claim 3. Additionally, we "paired off" the enzymes and diseases in claim 1 as suggested by the Examiner.

3. Written Description

3.1. Previously, claim 1 contemplated the treatment of any

disease caused by a deficiency of an enzyme belonging to the heme biosynthetic pathway, by means of a catalyst (especially an enzyme) of a step in that pathway. The enzymes were not then limited to human enzymes, but are now so limited.

The heme biosynthetic pathway is defined by the specification by reference to Sassa (1996), see P1, L22-27 and P7, L25-31. ALA synthetase is mentioned at P1, L24-25 and 31 and the other seven enzymes participating in this pathway are enumerated in the specification at P7, L25-31. The steps of the pathway are set forth in Sassa and are explained below:

	Substrate(s)	Enzyme	Product
(1)	succinyl Co, glycine	ALA synthase (synthetase)	(2)
(2)	ALA	ALA dehydratase	(3)
(3)	PBG	PBG deaminase (PBGD)	(4)
(4)	hydroxymethylbilane	uroporphyrinogen III cosynthase[1]	(5)
(5)	uroporphyrinogen III	uroporphyrinogen decarboxylase	(6)
(6)	coproporphyrinogen III	coproporphyrinogen oxidase	(7)
(7)	protoporphyrinogen IX	protoporphyrinogen oxidase	(8)
(8)	protoporphyrin IX	ferrochelatase	heme

The specification also disclosed nine human diseases related to reduced activities of these enzymes, see P8, L1-6.

At P8, L18-19, applicants specifically teach treatment of acute intermittent porphyria (AIP) with PBGD, and elsewhere they disclose two forms of human PBGD P15, L8-10. AIP is discussed in detail at PP 2-3.

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[1] This is identified as just "uroporphyrinogen III synthase" at P7, L30.

The Examiner appears to concede that the use of either form of PBGD to treat AIP is adequately described, but suggests that this constitute just two species of the genus. While the Examiner says that they are "representative", it is clear that the Examiner means to say that they are not representative.

However, this blithely ignores the disclosure of seven more enzymes and eight more diseases.

No human enzymes exist which belong to the heme biosynthetic pathway and are not identified as such in the specification. Nonetheless, to avoid any doubt, claim 1 has been amended to specifically recite the human enzymes (note that the two allelic forms of human PBGD count as one enzyme). Of course, the specification does not and cannot explicitly identify all allelic variants of each of these human enzymes. Nor should it be expected to make such identification, as it is evident that the range of allelic variation is small (typically a single lesion in each case). Thus, the known allelic forms (see Exs. A-1 to A-8) are representative of the genera of allelic forms of these enzymes.

We wish to make it clear that the term "human enzyme" is not intended to exclude production by recombinant DNA techniques in a nonhuman cell. It simply means that the amino acid sequence is that a natural human protein.

Claim 1 further limits the disease to one of nine disclosed porphyrias and recites a particular enzyme replacement therapy for each of the nine diseases. (Note that one enzyme is recited in connection with two different diseases.)

3.2. The Examiner also questioned description for (1) non-enzymatic catalysts, and (2) fragments and other mutants of naturally occurring enzymes. This is moot in view of the limitation of claim 1.

3.3. The issues specific to claims 21 and 22 are of course mooted by the cancellation of those claims.

4. Enablement Issues

The Examiner concedes that the specification is enabling for treatment or prophylaxis of AIP by administration of a PBGD encoded by SEQ ID NO:1 or 12. The Examiner questions enablement for treatment or prophylaxis of any disease resulting from a deficiency of one of the enzymes of the heme biosynthetic pathway, using one of those enzymes, or an enzymatically active fragment or analogue thereof.

As previously noted, claim 1 has been amended to excise coverage of enzymatically active fragments and analogues, and to expressly recite the nine diseases of former claim 2 and the eight enzymes of former claim 3.[2] Each of these recitations is intended to include enzymatically active allelic-variants of the enzyme, such as the two expressly disclosed variants of PBGD.

As pointed out in the specification, over 100 mutations in the PBGD gene have been identified (P38, L32-35). Some mutations are silent, others result in changes in the amino acid sequence of the encoded protein. Some of the non-silent mutations undoubtedly result in enzyme deficiency, and some undoubtedly are harmless. In general, the focus has been on identifying allelic variants associated with porphyria, rather than neutral (or positive) variants.

Table A on pp. 39-41 identifies 39 mutations which result in single substitution mutants at the protein level. These can readily be tested for retention of PBGD enzymatic activity, without undue experimentation.

Table A also identifies 12 frameshift mutations. These are unlikely to retain activity, because they affect a larger portion of the native sequence, but their activity is nonetheless readily testable.

Given the identification of so many allelic variants already, it is plain that identification of additional allelic variants of PBGD will not require undue experimentation. See Grandchamp (1996), cited at P38, L32-33, and references cited

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[2] While claim 3 may have appeared to list nine enzymes, two were listed twice.

therein. The more individuals screened, the more variants will become known. Neutral variants may be identified by screening normal individuals. PGBD 1.1 is a neutral variant.

With regard to the other enzymes of the human heme biosynthetic pathway, a search on the NIH database reveals that the sequences of all of these proteins was known (by virtue of gene sequencing) well before the 1998 priority date:

Enzyme	Genbank	Ref
ALA-synthase	P22557	Bishop, et al., Nucl. Acids. Res. 18:7187-8 **(1990)**
porphobilinogen deaminase	NP_000181	Raich **(1986)**
Delta-aminolevulinic acid dehydratase	P13716	Wetmur, PNAS 83:7703-7 **(1986)**
Uroporphyrinogen decarboxylase	NP_000365	Romeo, J. Biol. Chem., 261:9825-31 **(1986)**
coproporphyrinogen oxidase	NP_000088	Kohno, J. Biol. Chem., 268:21359-63 **(1993)**
protoporphyrinogen oxidase	NP_000300	Dailey, J. Biol. Chem., 269:813-5 **(1994)**
uroporphyrinogen III synthase	NP_000366	Tasi, PNAS 85:7049-53 **(1988)**
ferrochelatase	NP_000131	Nakahashi, PNAS 89:281-5 **(1992)**

Some of these proteins may also have been available even earlier, by isolation from natural sources. For example, Miyasi, et al., Proc. Nat. Acad. Sci. (USA) 76(12):6172-76 (1979) (Ref. CV) reported purification of uroporphyrinogen I synthase from human erythrocytes. It also notes that the cognate enzyme in bacteria, higher plants, and avian and mammalian erythrocytes had been purified previously.

The techniques used to identify allelic variants of PBGD may be applied to the identification of allelic variants of the other

recited enzymes.

Allelic variants giving rise to porphyrias have been identified for ALA-Synthase (Ex. A-1; 1992, 1994, 1998, 1999), ALA-dehydratase (Ex. A-2; 1991-92), PBG deaminase (Grandchamp ref. and Table A in specification and Ex. A-3), uroporphyrinogen III cosynthases (Ex. A-4; 1990, 1991); uroporphyrinogen decarboxylase (Ex. A-5; 1986, 1989, 1990, 1991, 1992, 1996, 1998); coproporphyrinogen oxidase (Ex. A-6; 1995, 1999, 2002); protoporphyrinogen oxidase (Ex. A-7; 1996, 1997, 1999, 2002) and ferrochelatase (Ex. A-8; 1992, 2002).

Allelic variants which encode enzymes with normal activity are identified by screening of individuals who do not suffer from porphyria.

In conclusion, there is ample support for the human enzymes[3] (including allelic variants now recited in claim 1, and for their use in connection with the treatment or prophylaxis of a porphyria.

5. Prior Art Issues

5.1. The examiner contends that it would have been obvious in 1998 to use the porphobilinogen deaminase (PBGD) gene of Raich et al. (1986) to treat the genetic disease acute intermittent porphyria (AIP), known from Raich to be attributable to PBGD deficiency, in view of many publications on enzyme replacement therapy, notably Beutler (1991).

We argued that this prima facie case was rebutted by the showing of a longfelt need for a therapy for AIP, coupled with a longterm failure of others to apply replacement therapy for AIP. We showed that replacement therapy has been known since 1966, that the connection between PBGD and AIP has been known since 1972, and that the PBGD gene has been known since 1986.

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[3] We remind the Examiner that the claim covers use of either the purified natural enzyme, or an artificial enzyme, with the same amino acid sequence, which is recombinantly produced. The recombinant protein of course must retain the enzymatic activity of its natural counterpart.

(Our priority application was filed in 1998, twelve years later.)

With regard to the connection between PBGD deficiency and AIP, we said that Raich (1986) was parrotting the teachings of his reference (2), which is Meyer (1972). The Examiner completely misinterprets this remark.

We were not arguing that Raich (1986) was not prior art because it parroted Meyer. Rather we were showing that if the Examiner's inference of obviousness was correct, those skilled in the art should have been seeking to intervene against AIP by attacking PBGD since 1972 (Meyer's publication year), whereas instead the drugs for AIP have targeted ALA-synthetase/circulating heme.

Likewise we were not arguing that Beutler (1991) was not prior art, but rather that replacement therapy was an even older concept.

Ultimately, the question was, if (1) replacement therapy was the obvious solution to genetic disease (2) AIP was known to be a genetic disease, (3) PBGD deficiency was known to be a risk factor for AIP, and (4) the PBGD gene was known, why didn't the art use PBGD for replacement therapy of AIP during the twelve years between Raich's sequencing of the gene and our priority application? For that matter, why didn't the art isolate and characterize the pbgd gene soon after Meyer revealed (in 1972) its relevance to AIP?

In Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1965) the Supreme Court held that "such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized" as indicia of nonobviousness. These considerations are "secondary" only in the sense that they are factual inquiries leading to the ultimate conclusion of law. Consequently, the courts now refer to these factors as "objective considerations", not "secondary" ones. See, e.g., WMS Gaming Inc. v. International Game Technology, 51 USPQ2d 1385, 1396 (Fed. Cir. 1999).

In Strataflex, Inc. v. Aeroquip Corp., 218 USPQ 871, 879

(Fed. Cir. 1983), the Court commented

> It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness.... Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art".28

Hence, it is "necessary" that these secondary considerations be evaluated, even at the examination stage. According to In re Sernaker, 217 USPQ 1 (Fed. Cir. 1983),

> "In an appeal of a rejection of a patent application, secondary considerations, such as commercial success, typically do not play a large part in the analysis of obviousness because the inventor usually waits until his patent issues before he swings production into full gear. Thus, a detailed analysis of secondary considerations is more common in cases like John Deere, which involved infringement. If, however, a patent application properly presents evidence relating to these secondary considerations, the board must always consider such evidence in connection with the determination of obviousness."

And this must be done in every case, not just when the case seems "close". In In re Piasecki, 223 USPQ 785 (Fed. Cir. 1984), the Federal Circuit criticized the board for declining to give weight to rebuttal evidence relating to "secondary considerations".

The renowned jurist Learned Hand viewed "the length of time the art, though needing the invention, went without it" as the

best basis for inferring nonobviousness. Judge Easterbrook noted,

> "The existence of an enduring, unmet need is strong evidence that the invention is novel, not obvious, and not anticipated. If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence--the kind that can't be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences--of the state of knowledge."

In In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988), USP 3,919,354, (effective filing date of 1971-72) subjected to reexamination, was rejected as obvious over Molau et al. (1966) and Baer USP 2,971,939 (issued 1961). The Board sustained the rejection, but the Federal Circuit reversed. The issue was whether it would have been obvious in 1971-72 to make a resin which combined Baer's styrene and maleic anhydride copolymer (which had improved heat resistance) with Molau's diene rubber, by Baer's process. The Court held that there was evidence of a longfelt need for a rubber with improved heat resistance, and noted that skepticism was expressed as to whether the claimed three component product could be made. Applicants note that five years elapsed, without the need being met by another, between the publication of Molau et al. and the filing of the first application leading to the '354 patent. Clearly, five years qualified as "longfelt".

In Allen Archery, Inc. v. Browning Manufacturing Co., 226 USPQ 315 (D. Utah 1985), aff'd, 2 USPQ2d 1490 (Fed. Cir. 1987), the Allen compound bow was the subject of an application filed in 1966. The principal references against the patent were Barna USP 2,957,470 and Wilkerson 2,957,469, both of which issued on October 25, 1960. The Federal Circuit agreed that the Allen compound bow "fulfilled a longfelt need in the field of archery", 2 USPQ2d at 1493, even though the Allen application was filed only six years after the reference date.

In Boots Laboratories, Inc. v. Burroughs Wellcome Co., 223 UPSQ 840 (E.D. Va. 1984), the district court observed that the concept of inhibiting xanthine oxidase as a potential treatment for gout had existed since at least 1945 (finding C2). Failed attempts were made in that year and again in 1952 and 1956. The patent in suit claimed a 1955 British priority, but was accorded an effective filing date of 1962, 223 USPQ at 847. The district court held that the patentee had fulfilled a longfelt need.

In Tech Air, Inc. v. Denso Mfg. Mach., Inc., 193 F.3d 1353, 52 USPQ2d 1294 (Fed. Cir. 1999), the Federal Circuit upheld a holding of nonobviousness:

> According to the trial court, Tec Air also offered testimony that "there was a long-felt but unmet need to create a more efficient method to achieve fan balance" prior to the Swin patents. Swin, Sr. testified that Tec Air used several unsatisfactory balancing techniques before adopting the patented one. Dr. Williamson testified that the industry experienced problems with the prior art machining methods. Moreover, after Denso ceased infringing the Swin patents, it had to resort to less effective methods of balancing the fans. Based on this evidence, the jury reasonably could have found there was a long-felt but unmet need in the prior art for an improved balancing method, which the Swin patents satisfied.

See also WMS Gaming Inc. v. Int'l Game Tech., 184 F.3d 1339, 51 USPQ2d 1385 (Fed. Cir. 1999); A1-Site Corp. v. VSI Int'l., Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (eyeglass hangers); Armament Sys. Procedures v. Monadnock Lifetime Prods., 1998 U.S. App. LEXIS 20818 (August 7, 1998), reh. denied, 1998 U.S. App. LEXIS 24605; Modine Mfg. Co. v. U.S.I.T.C, 75 F.3d 1545, 37 USPQ2d 1609 (Fed. Cir. 1996) (automotive condenser); Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., 21 F.3d 1068, 30 USPQ2d 1377 (Fed. Cir. 1994) (printing press); Stiflung v. Renishow PLC, 945 F.2d 1173, 20 USPQ2d 1094 (1991)

(coordinate measuring machine probe; trial court holding of obviousness reversed); Hughes Tool Co. v. Dresser Industries, Inc., 816 F.2d 1549, 2 USPQ 2d 1396, 1397 (Fed. Cir. 1987) (drilling bit); Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 221 USPQ 669 (Fed. Cir 1984); Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 221 USPQ1 (Fed. Cir. 1984); Jones v. Hardy, 727 F.d2 1524, 220 USPQ 1021 (Fed. Cir. 1984); Poly-America, L.P. v. GSE Lining Tech., Inc., 2003 U.S. Dist. LEXIS 14130 (August 13, 2003); Nat's Steel Car, Ltd. v. Canadian Pacific Railway Co., 249 F. Supp. 2d 1346 (N.D. Ga. 2003); Tate Access Floors, Inc. v. Interface Architectural Res., Inc., 185 F. Supp.2d 588 (D. Md. 2002); Bose Corp. v. Jbl, Inc., 112 F. Supp.2d 138 (D. Mas. 2000), aff'd 274 F.3d 1354, 61 USPQ 2d 1216 (Fed. Cir. 2001); Lawler Mfg. Co. v. Bradley Corp., 2000 U.S. Dist. LEXIS 14198 (S. D. Ind. 2000); TC Mfg. Co. v. Polyguard Products, 2000 U.S. Dist. LEXIS 11487 (N.D. Ill. 2000); Lifescan, Inc. v. Home Diagnostics, Inc., 103 F. Supp.2d 345 (D. Del. 2000); Alcon Laboratories, Inc. v. Bausch & Lomb, Inc., 52 USPQ2d 1927 (N.D. Tex. 1999) (Tobradex); Novo Nordisk of N. Am. v. Genentech, 1995 U.S. Dist. LEXIS 12588 (S.D.N.Y. 1995) (hGH); Henkel Corp. v. Coral, Inc., 754 F. Supp. 1280, 21 USPQ2d 1081 (N.D. Ill. 1990); Upjohn Co. v. Medtron Laboratories, Inc., 751 F. Supp. 416, 17 USPQ2d 1268 (S.D.N.Y. 1990) (Minoxidil); American Standard, Inc. v. Pfizer, Inc., 722 F. Supp. 86, 14 USPQ2d 1673 (D. Del. 1989) (orthopedic implants); U.S. Surgical Corp. v. Hospital Products Intl. pty. Ltd., 701 F. Supp. 314, 9 USPQ2d 1241 (D. Conn. 1988) (surgical stapling); Hallburton Co. v. Western Co. of North America, 10 USPQ2d 1973 (W.D. Okla. 1988); Crucible, Inc. v. Sterra Kopparbergs Bergslags AB, 594 F. Supp. 1249, 226 USPQ 36, 266 USPQ 36 (W.D. Pa. 1984); Eli Lilly Co. v. Premo Pharm. Labs., Inc., 1979 U.S. Dist. LEXIS 11039 (D.N.J. 1979) (cephalexin); Zenith Laboratories, Inc. v. Eli Lilly & co., 460 F. Supp. 812, 201 USPQ 324 (D.N.J. 1978)

(Darvon); Reynolds Metals Co. v. ALCOA, 457 F. Supp. 482, 198 USPQ 529 (N.D. Ind. 1978).

Respectfully submitted,

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Enclosures
-Exs. A-1 to A-8 (NIH database extracts)

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IPC:lms
G:\ipc\n-q\Plou\fogh1\pto amend2.wpd

☐ 1: P22557. 5-aminolevulinic ...[gi:20141346]

BLink, Domains, Links

LOCUS P22557 587 aa linear PRI 15-MAR-2004
DEFINITION 5-aminolevulinic acid synthase, erythroid-specific, mitochondrial precursor (Delta-aminolevulinate synthase) (Delta-ALA synthetase) (ALAS-E).
ACCESSION P22557
VERSION P22557 GI:20141346
DBSOURCE swissprot: locus HEMO_HUMAN, accession P22557;
class: standard.
extra accessions:Q13735,created: Aug 1, 1991.
sequence updated: Feb 28, 2003.
annotation updated: Mar 15, 2004.
xrefs: gi: 28585, gi: 28586, gi: 28587, gi: 28588, gi: 3220248, gi: 3220249, gi: 1869771, gi: 3150091, gi: 2144401
xrefs (non-sequence databases): HSSPP12998, GenewHGNC:397, MIM 301300, GO0006783, InterProIPR003408, InterProIPR004839, InterProIPR001917, PfamPF02490, PfamPF00155, PROSITEPS00599
KEYWORDS Heme biosynthesis; Transferase; Acyltransferase; Mitochondrion; Transit peptide; Pyridoxal phosphate; Multigene family; Disease mutation.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 587)
AUTHORS Bishop,D.F.
TITLE Two different genes encode delta-aminolevulinate synthase in humans: nucleotide sequences of cDNAs for the housekeeping and erythroid genes
JOURNAL Nucleic Acids Res. 18 (23), 7187-7188 (1990)
MEDLINE 91088347
PUBMED 2263504
REMARK SEQUENCE FROM N.A.
TISSUE=Liver
REFERENCE 2 (residues 1 to 587)
AUTHORS Cox,T.C., Bawden,M.J., Martin,A. and May,B.K.
TITLE Human erythroid 5-aminolevulinate synthase: promoter analysis and identification of an iron-responsive element in the mRNA
JOURNAL EMBO J. 10 (7), 1891-1902 (1991)
MEDLINE 91266919
PUBMED 2050125
REMARK SEQUENCE FROM N.A.
TISSUE=Liver
REFERENCE 3 (residues 1 to 587)
AUTHORS Surinya,K.H., Cox,T.C. and May,B.K.
TITLE Identification and characterization of a conserved erythroid-specific enhancer located in intron 8 of the human 5-aminolevulinate synthase 2 gene
JOURNAL J. Biol. Chem. 273 (27), 16798-16809 (1998)
MEDLINE 98307914
PUBMED 9642238
REMARK SEQUENCE FROM N.A.
REFERENCE 4 (residues 1 to 587)

AUTHORS Isherwood,J. and Bird,C.
TITLE Direct Submission
JOURNAL Submitted (~MAY-1998)
REMARK SEQUENCE FROM N.A.
REFERENCE 5 (residues 1 to 587)
AUTHORS Cox,T.C., Bottomley,S.S., Wiley,J.S., Bawden,M.J., Matthews,C.S. and May,B.K.
TITLE X-linked pyridoxine-responsive sideroblastic anemia due to a Thr388-to-Ser substitution in erythroid 5-aminolevulinate synthase
JOURNAL N. Engl. J. Med. 330 (10), 675-679 (1994)
MEDLINE 94150519
PUBMED 8107717
REMARK VARIANT XLSA SER-388.
REFERENCE 6 (residues 1 to 587)
AUTHORS Cotter,P.D., Baumann,M. and Bishop,D.F.
TITLE Enzymatic defect in 'X-linked' sideroblastic anemia: molecular evidence for erythroid delta-aminolevulinate synthase deficiency
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 89 (9), 4028-4032 (1992)
MEDLINE 92237301
PUBMED 1570328
REMARK VARIANT XLSA ASN-476.
REFERENCE 7 (residues 1 to 587)
AUTHORS Furuyama,K., Uno,R., Urabe,A., Hayashi,N., Fujita,H., Kondo,M., Sassa,S. and Yamamoto,M.
TITLE R411C mutation of the ALAS2 gene encodes a pyridoxine-responsive enzyme with low activity
JOURNAL Br. J. Haematol. 103 (3), 839-841 (1998)
MEDLINE 99073953
PUBMED 9858242
REMARK VARIANT XLSA CYS-411.
REFERENCE 8 (residues 1 to 587)
AUTHORS Harigae,H., Furuyama,K., Kudo,K., Hayashi,N., Yamamoto,M., Sassa,S. and Sasaki,T.
TITLE A novel mutation of the erythroid-specific gamma-Aminolevulinate synthase gene in a patient with non-inherited pyridoxine-responsive sideroblastic anemia
JOURNAL Am. J. Hematol. 62 (2), 112-114 (1999)
MEDLINE 20012168
PUBMED 10577279
REMARK VARIANT XLSA GLN-204.
REFERENCE 9 (residues 1 to 587)
AUTHORS Cotter,P.D., May,A., Li,L., Al-Sabah,A.I., Fitzsimons,E.J., Cazzola,M. and Bishop,D.F.
TITLE Four new mutations in the erythroid-specific 5-aminolevulinate synthase (ALAS2) gene causing X-linked sideroblastic anemia: increased pyridoxine responsiveness after removal of iron overload by phlebotomy and coinheritance of hereditary hemochromatosis
JOURNAL Blood 93 (5), 1757-1769 (1999)
MEDLINE 99155356
PUBMED 10029606
REMARK VARIANTS XLSA HIS-199; CYS-411; GLN-448 AND CYS-452.
COMMENT On Apr 11, 2002 this sequence version replaced gi:122816.

[CATALYTIC ACTIVITY] Succinyl-CoA + glycine = 5-aminolevulinate + CoA + CO(2).
[COFACTOR] Pyridoxal phosphate.
[PATHWAY] Heme biosynthesis; first (rate-limiting) step.
[SUBUNIT] Homodimer.
[SUBCELLULAR LOCATION] Mitochondrial matrix.

[TISSUE SPECIFICITY] Erythroid specific.
[DISEASE] Defects in ALAS2 are a cause of X-linked sideroblastic anemia (XLSA) [MIM:301300]. Sideroblastic anemia is characterized by anemia of varying severity, hypochromic peripheral erythrocytes, progressive accumulation of iron, and the presence of ringed sideroblasts in the bone marrow.
[MISCELLANEOUS] There are two delta-ALA synthetase in vertebrates: an erythroid- specific form and one (housekeeping) which is expressed in all tissues.
[SIMILARITY] Belongs to class-II of pyridoxal-phosphate-dependent aminotransferases.

FEATURES	Location/Qualifiers
source	1..587 /organism="Homo sapiens" /db_xref="taxon:9606"
gene	1..587 /gene="ALAS2" /note="synonyms: ALASE, ASB"
Protein	1..587 /gene="ALAS2" /product="5-aminolevulinic acid synthase, erythroid-specific, mitochondrial precursor" /EC_number="2.3.1.37"
Region	(1.586)..587 /gene="ALAS2" /region_name="Mature chain" /note="5-aminolevulinic acid synthase, erythroid-specific."
Region	1..(2.587) /gene="ALAS2" /region_name="Transit peptide" /note="Mitochondrion."
Region	182 /gene="ALAS2" /region_name="Conflict" /note="S -> F (in Ref. 1)."
Region	199 /gene="ALAS2" /region_name="Variant" /note="Y -> H (in XLSA). /FTId=VAR_012334."
Region	204 /gene="ALAS2" /region_name="Variant" /note="R -> Q (in XLSA; 15% to 35% activity of wild-type). /FTId=VAR_012335."
Region	388 /gene="ALAS2" /region_name="Variant" /note="T -> S (in XLSA). /FTId=VAR_000562."
Site	391 /gene="ALAS2" /site_type="binding" /note="Pyridoxal phosphate (Probable)."
Region	411 /gene="ALAS2" /region_name="Variant" /note="R -> C (in XLSA; 12% to 25% activity of wild-type). /FTId=VAR_000563."
Region	448 /gene="ALAS2" /region_name="Variant" /note="R -> Q (in XLSA). /FTId=VAR_012336."
Region	452 /gene="ALAS2" /region_name="Variant"

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                     /note="R -> C (in XLSA). /FTId=VAR_012057."
     Region.         476
                     /gene="ALAS2"
                     /region_name="Variant"
                     /note="I -> N (in XLSA). /FTId=VAR_000564."
ORIGIN
        1 mvtaamllqc cpvlargpts llgkvvkthq flfgigrcpi latqgpncsq ihlkatkagg
       61 dspswakghc pfmlselqdg kskivqkaap evqedvkafk tdlpsslvsv slrkpfsgpq
      121 eqeqisgkvt hliqnnmpgn yvfsydqffr dkimekkqdh tyrvfktvnr wadaypfaqh
      181 fseasvaskd vsvwcsndyl gmsrhpqvlq atqetlqrhg agaggtrnis gtskfhvele
      241 qelaelhqkd sallfsscfv andstlftla kilpgceiys dagnhasmiq girnsgaakf
      301 vfrhndpdhl kklleksnpk ipkivafetv hsmdgaicpl eelcdvshqy galtfvdevh
      361 avglygsrga gigerdgimh kidiisgtlg kafgcvggyi astrdlvdmv rsyaagfift
      421 tslppmvlsg alesvrllkg eegqalrrah qrnvkhmrql lmdrglpvip cpshiipirv
      481 gnaalnsklc dlllskhgiy vqainyptvp rgeellrlap sphhspqmme dfveklllaw
      541 tavglplqdv svaacnfcrr pvhfelmsew ersyfgnmgp qyvttya
//
```

1: P13716. Delta-aminolevuli...[gi:122833] BLink, Domains, Links

LOCUS P13716 330 aa linear PRI 15-MAR-2004
DEFINITION Delta-aminolevulinic acid dehydratase (Porphobilinogen synthase) (ALADH).
ACCESSION P13716
VERSION P13716 GI:122833
DBSOURCE swissprot: locus HEM2_HUMAN, accession P13716;
class: standard.
extra accessions:Q16870,Q16871,created: Jan 1, 1990.
sequence updated: Jan 1, 1990.
annotation updated: Mar 15, 2004.
xrefs: gi: 178328, gi: 178329, gi: 28579, gi: 28580, gi: 248838, gi: 248839, gi: 248840, gi: 248841, gi: 34192221, gi: 34192222, gi: 88408, pdb accession 1E51
xrefs (non-sequence databases): SWISS-2DPAGEP13716, GenewHGNC:395, MIM 125270, GO0003824, GO0004655, GO0006783, InterProIPR001731, PfamPF00490, PRINTSPR00144, ProDomPD002304, PROSITEPS00169
KEYWORDS Porphyrin biosynthesis; Heme biosynthesis; Lyase; Zinc; Disease mutation; Polymorphism; 3D-structure.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 330)
AUTHORS Wetmur,J.G., Bishop,D.F., Cantelmo,C. and Desnick,R.J.
TITLE Human delta-aminolevulinate dehydratase: nucleotide sequence of a full-length cDNA clone
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 83 (20), 7703-7707 (1986)
MEDLINE 87017017
PUBMED 3463993
REMARK SEQUENCE FROM N.A.
REFERENCE 2 (residues 1 to 330)
AUTHORS Wetmur,J.
TITLE RsaI polymorphism in the human delta-aminolevulinate dehydratase gene at 9q34
JOURNAL Nucleic Acids Res. 19, 4307-4307 (1991)
REMARK SEQUENCE FROM N.A.
TISSUE=Liver
REFERENCE 3 (residues 1 to 330)
AUTHORS Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G., Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D., Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K., Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F., Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L., Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L., Scheetz,T.E., Brownstein,M.J., Usdin,T.B., Toshiyuki,S., Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J., Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J., McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S., Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W., Villalon,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A., Fahey,J., Helton,E., Ketteman,M., Madan,A., Rodrigues,S., Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y.,

Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D., Dickson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M., Butterfield,Y.S.N., Krzywinski,M.I., Skalska,U., Smailus,D.E., Schnerch,A., Schein,J.E., Jones,S.J.M. and Marra,M.A.

TITLE Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences

JOURNAL Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)

MEDLINE 22388257

PUBMED 12477932

REMARK SEQUENCE FROM N.A.
TISSUE=Placenta

REFERENCE 4 (residues 1 to 330)

AUTHORS Gibbs,P.N. and Jordan,P.M.

TITLE Identification of lysine at the active site of human 5-aminolaevulinate dehydratase

JOURNAL Biochem. J. 236 (2), 447-451 (1986)

MEDLINE 86323088

PUBMED 3092810

REMARK ACTIVE SITE.

REFERENCE 5 (residues 1 to 330)

AUTHORS Mills-Davies,N.L., Thompson,D., Cooper,J.B. and Shoolingin-Jordan,P.M.

TITLE Direct Submission

JOURNAL Submitted (~OCT-1998) to the PDB data bank

REMARK X-RAY CRYSTALLOGRAPHY (2.83 ANGSTROMS).

REFERENCE 6 (residues 1 to 330)

AUTHORS Wetmur,J.G., Kaya,A.H., Plewinska,M. and Desnick,R.J.

TITLE Molecular characterization of the human delta-aminolevulinate dehydratase 2 (ALAD2) allele: implications for molecular screening of individuals for genetic susceptibility to lead poisoning

JOURNAL Am. J. Hum. Genet. 49 (4), 757-763 (1991)

MEDLINE 91377738

PUBMED 1716854

REMARK VARIANT ASN-59.

REFERENCE 7 (residues 1 to 330)

AUTHORS Plewinska,M., Thunell,S., Holmberg,L., Wetmur,J.G. and Desnick,R.J.

TITLE delta-Aminolevulinate dehydratase deficient porphyria: identification of the molecular lesions in a severely affected homozygote

JOURNAL Am. J. Hum. Genet. 49 (1), 167-174 (1991)

MEDLINE 91290050

PUBMED 2063868

REMARK VARIANTS ARG-133 AND MET-275.

REFERENCE 8 (residues 1 to 330)

AUTHORS Ishida,N., Fujita,H., Fukuda,Y., Noguchi,T., Doss,M., Kappas,A. and Sassa,S.

TITLE Cloning and expression of the defective genes from a patient with delta-aminolevulinate dehydratase porphyria

JOURNAL J. Clin. Invest. 89 (5), 1431-1437 (1992)

MEDLINE 92235256

PUBMED 1569184

REMARK VARIANTS TRP-240 AND THR-274.

COMMENT ---

[CATALYTIC ACTIVITY] 2 5-aminolevulinate = porphobilinogen + 2 H(2)O.
[COFACTOR] Zinc.
[PATHWAY] Porphyrin and heme biosynthesis; second step.
[SUBUNIT] Homooctamer.
[POLYMORPHISM] There are two common alleles of ALAD. Individuals

heterozygous or homozygous for ALAD*2 Asn-59 have significantly higher blood lead levels than do ALAD*1 Lys-59 homozygotes when exposed to environmental lead.
[DISEASE] Defects in ALAD are the cause of acute hepatic porphyria [MIM:125270].
[SIMILARITY] Belongs to the ALADH family.

FEATURES	Location/Qualifiers
source	1..330 /organism="Homo sapiens" /db_xref="taxon:9606"
gene	1..330 /gene="ALAD"
Protein	1..330 /gene="ALAD" /product="Delta-aminolevulinic acid dehydratase" /EC_number="4.2.1.24"
Region	3..4 /gene="ALAD" /region_name="Hydrogen bonded turn"
Region	8..10 /gene="ALAD" /region_name="Helical region"
Region	14..19 /gene="ALAD" /region_name="Helical region"
Region	20..23 /gene="ALAD" /region_name="Hydrogen bonded turn"
Region	28..30 /gene="ALAD" /region_name="Helical region"
Region	31..38 /gene="ALAD" /region_name="Beta-strand region"
Region	41..42 /gene="ALAD" /region_name="Hydrogen bonded turn"
Region	46..47 /gene="ALAD" /region_name="Beta-strand region"
Region	51..52 /gene="ALAD" /region_name="Hydrogen bonded turn"
Region	53..56 /gene="ALAD" /region_name="Beta-strand region"
Region	58..70 /gene="ALAD" /region_name="Helical region"
Region	59 /gene="ALAD" /region_name="Variant" /note="K -> N (in allele ALAD*2; 10% of population; dbSNP:1800435). /FTId=VAR_003633."
Region	71..72 /gene="ALAD" /region_name="Hydrogen bonded turn"
Region	75..81 /gene="ALAD" /region_name="Beta-strand region"
Region	95..96 /gene="ALAD" /region_name="Hydrogen bonded turn"
Region	100..111 /gene="ALAD"

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Region	113..114
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	/region_name="Hydrogen bonded turn"
Region	116..121
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	/region_name="Beta-strand region"
Site	122
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	/note="Zinc (catalytic)."
Site	124
	/gene="ALAD"
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	/note="Zinc (catalytic)."
Site	132
	/gene="ALAD"
	/site_type="metal-binding"
	/note="Zinc (catalytic)."
Region	133
	/gene="ALAD"
	/region_name="Variant"
	/note="G -> R (in acute hepatic porphyria).
	/FTId=VAR_003634."
Region	141
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Region	143..159
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Region	160..161
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	/region_name="Hydrogen bonded turn"
Region	164..167
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	/region_name="Beta-strand region"
Region	172..173
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Region	174..184
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Region	185..186
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Region	188..190
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Region	192..194
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Region	198..200
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Region	221..223
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Region	224
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Region               226
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Region               231..243
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Region               240
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                     /region_name="Variant"
                     /note="R -> W (in acute hepatic porphyria).
                     /FTId=VAR_003635."
Region               244..245
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Region               248..252
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Site                 252
                     /gene="ALAD"
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Region               255..257
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Region               258..267
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Region               269..270
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Region               273..277
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                     /region_name="Beta-strand region"
Region               274
                     /gene="ALAD"
                     /region_name="Variant"
                     /note="A -> T (in acute hepatic porphyria).
                     /FTId=VAR_003636."
Region               275
                     /gene="ALAD"
                     /region_name="Variant"
                     /note="V -> M (in acute hepatic porphyria).
                     /FTId=VAR_003637."
Region               279..290
                     /gene="ALAD"
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Region               291..292
                     /gene="ALAD"
                     /region_name="Hydrogen bonded turn"
Region               296..310
                     /gene="ALAD"
                     /region_name="Helical region"
Region               311
                     /gene="ALAD"
                     /region_name="Hydrogen bonded turn"
Region               314..317
                     /gene="ALAD"
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Region               318..319
                     /gene="ALAD"
                     /region_name="Hydrogen bonded turn"
Region               320..326
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                     /region_name="Helical region"
     Region          327
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                     /region_name="Hydrogen bonded turn"
ORIGIN
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       61 leemlrplve eglrcvlifg vpsrvpkder gsaadseesp aieaihllrk tfpnllvacd
      121 vclcpytshg hcgllsenga fraeesrqrl aevalayaka gcqvvapsdm mdgrveaike
      181 almahglgnr vsvmsysakf ascfygpfrd aaksspafgd rrcyqlppga rglalravdr
      241 dvregadmlm vkpgmpyldi vrevkdkhpd lplavyhvsg efamlwhgaq agafdlkaav
      301 leamtafrra gadiiityyt pqllqwlkee
//
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A-3

1: NP_000181. hydroxymethylbila...[gi:20149500] BLink, Domains, Links

LOCUS NP_000181 361 aa linear PRI 21-DEC-2003
DEFINITION hydroxymethylbilane synthase; porphobilinogen deaminase [Homo sapiens].
ACCESSION NP_000181
VERSION NP_000181.2 GI:20149500
DBSOURCE REFSEQ: accession NM_000190.2
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 361)
AUTHORS King,P.H., Petersen,N.E., Rakhra,R. and Schreiber,W.E.
TITLE Porphyria presenting with bilateral radial motor neuropathy: evidence of a novel gene mutation
JOURNAL Neurology 58 (7), 1118-1121 (2002)
PUBMED 11940707
REMARK GeneRIF: A novel mutation of the PBGD gene has been identified in a patient with acute intermittent porphyria presenting with severe and bilateral axonal radial motor neuropathy.
REFERENCE 2 (residues 1 to 361)
AUTHORS Gregor,A., Schneider-Yin,X., Szlendak,U., Wettstein,A., Lipniacka,A., Rufenacht,U.B. and Minder,E.I.
TITLE Molecular study of the hydroxymethylbilane synthase gene (HMBS) among Polish patients with acute intermittent porphyria
JOURNAL Hum. Mutat. 19 (3), 310 (2002)
PUBMED 11857754
REMARK GeneRIF: 40% of all mutations identified among the Polish acute intermittent porphyria (AIP)patients in this study are novel, indicating the heterogeneity of molecular defects causing AIP.
REFERENCE 3 (residues 1 to 361)
AUTHORS Martinez di Montemuros,F., Di Pierro,E., Biolcati,G., Rocchi,E., Bissolotti,E., Tavazzi,D., Fiorelli,G. and Cappellini,M.D.
TITLE Acute intermittent porphyria: heterogeneity of mutations in the hydroxymethylbilane synthase gene in Italy
JOURNAL Blood Cells Mol. Dis. 27 (6), 961-970 (2001)
PUBMED 11831862
REMARK GeneRIF: In Italy, molecular analysis of the HMBS gene in acute intermittent porphyria patients and in family members of Italian ancestry identified 13 different mutations among 14 patients; 7 are new findings.
REFERENCE 4 (residues 1 to 361)
AUTHORS Davies,B. and Fried,M.
TITLE The structure of the human intron-containing S8 ribosomal protein gene and determination of its chromosomal location at 1p32-p34.1
JOURNAL Genomics 15 (1), 68-75 (1993)
PUBMED 8432552
REFERENCE 5 (residues 1 to 361)
AUTHORS Lander,M., Pitt,A.R., Alefounder,P.R., Bardy,D., Abell,C. and Battersby,A.R.
TITLE Studies on the mechanism of hydroxymethylbilane synthase concerning the role of arginine residues in substrate binding

JOURNAL Biochem. J. 275 (Pt 2), 447-452 (1991)
PUBMED 2025226
REFERENCE 6 (residues 1 to 361)
AUTHORS Tunnacliffe,A. and McGuire,R.S.
TITLE A physical linkage group in human chromosome band 11q23 covering a region implicated in leukocyte neoplasia
JOURNAL Genomics 8 (3), 447-453 (1990)
PUBMED 1981047
REFERENCE 7 (residues 1 to 361)
AUTHORS Grandchamp,B., De Verneuil,H., Beaumont,C., Chretien,S., Walter,O. and Nordmann,Y.
TITLE Tissue-specific expression of porphobilinogen deaminase. Two isoenzymes from a single gene
JOURNAL Eur. J. Biochem. 162 (1), 105-110 (1987)
PUBMED 3816774
REFERENCE 8 (residues 1 to 361)
AUTHORS Raich,N., Romeo,P.H., Dubart,A., Beaupain,D., Cohen-Solal,M. and Goossens,M.
TITLE Molecular cloning and complete primary sequence of human erythrocyte porphobilinogen deaminase
JOURNAL Nucleic Acids Res. 14 (15), 5955-5968 (1986)
PUBMED 2875434
COMMENT PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from BC019323.1. On Apr 15, 2002 this sequence version replaced gi:4504423.

Summary: Acute intermittent porphyria is inherited as an autosomal dominant disorder and is characterized by recurrent attacks of abdominal pain, gastrointestinal dysfunction, neurologic disturbances, and excessive amounts of aminolevulinic acid and porphobilinogen in the urine. AIP results from an error in pyrrole metabolism due to deficiency of porphobilinogen deaminase (EC 4.3.1.8). [supplied by OMIM].

FEATURES Location/Qualifiers

source 1..361
/organism="Homo sapiens"
/db_xref="taxon:9606"
/chromosome="11"
/map="11q23.3"

Protein 1..361
/product="hydroxymethylbilane synthase"
/EC_number="4.3.1.8"
/note="porphobilinogen deaminase"

Region 15..332
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/note="KOG2892"
/db_xref="CDD:20678"

variation 153
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/replace="Q"
/db_xref="dbSNP:694328"

variation 177
/replace="L"
/replace="M"
/db_xref="dbSNP:762585"

CDS 1..361
/gene="HMBS"
/coded_by="NM_000190.2:152..1237"
/note="go_function: hydroxymethylbilane synthase activity [goid 0004418] [evidence TAS] [pmid 2025226]; go_function: lyase activity [goid 0016829] [evidence IEA]; go_process: heme biosynthesis [goid 0006783] [evidence IEA]"
/db_xref="GeneID:3145"

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                     /db_xref="MIM:176000"
ORIGIN
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      121 davvfhpkfv gktletlpek svvgtsslrr aaqlqrkfph lefrsirgnl ntrlrkldeq
      181 qefsaiilat aglqrmgwhn rvgqilhpee cmyavgqgal gvevrakdqd ildlvgvlhd
      241 petllrciae raflrhlegg csvpvavhta mkdgqlyltg gvwsldgsds iqetmqatih
      301 vpaqhedgpe ddpqlvgita rniprgpqla aqnlgislan lllskgakni ldvarqlnda
      361 h
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A-4

1: NP_000366. uroporphyrinogen ...[gi:4557873] BLink, Domains, Links

LOCUS NP_000366 265 aa linear PRI 20-DEC-2003
DEFINITION uroporphyrinogen III synthase [Homo sapiens].
ACCESSION NP_000366
VERSION NP_000366.1 GI:4557873
DBSOURCE REFSEQ: accession NM_000375.1
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 265)
AUTHORS Aizencang,G., Solis,C., Bishop,D.F., Warner,C. and Desnick,R.J.
TITLE Human uroporphyrinogen-III synthase: genomic organization, alternative promoters, and erythroid-specific expression
JOURNAL Genomics 70 (2), 223-231 (2000)
PUBMED 11112350
REFERENCE 2 (residues 1 to 265)
AUTHORS Astrin,K.H., Warner,C.A., Yoo,H.W., Goodfellow,P.J., Tsai,S.F. and Desnick,R.J.
TITLE Regional assignment of the human uroporphyrinogen III synthase (UROS) gene to chromosome 10q25.2----q26.3
JOURNAL Hum. Genet. 87 (1), 18-22 (1991)
PUBMED 2037278
REFERENCE 3 (residues 1 to 265)
AUTHORS Deybach,J.C., de Verneuil,H., Boulechfar,S., Grandchamp,B. and Nordmann,Y.
TITLE Point mutations in the uroporphyrinogen III synthase gene in congenital erythropoietic porphyria (Gunther's disease)
JOURNAL Blood 75 (9), 1763-1765 (1990)
PUBMED 2331520
REFERENCE 4 (residues 1 to 265)
AUTHORS Tsai,S.F., Bishop,D.F. and Desnick,R.J.
TITLE Human uroporphyrinogen III synthase: molecular cloning, nucleotide sequence, and expression of a full-length cDNA
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 85 (19), 7049-7053 (1988)
PUBMED 3174619
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from J03824.1.

Summary: The protein encoded by this gene catalyzes the fourth step of porphyrin biosynthesis in the heme biosynthetic pathway. Defects in this gene cause congenital erythropoietic porphyria (Gunther's disease).

FEATURES Location/Qualifiers
source 1..265
/organism="Homo sapiens"
/db_xref="taxon:9606"
/chromosome="10"
/map="10q25.2-q26.3"
Protein 1..265
/product="uroporphyrinogen III synthase"
/EC_number="4.2.1.75"

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     Region          1..26
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                     [Coenzyme transport and metabolism]"
                     /note="KOG4132"
                     /db_xref="CDD:21910"
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                     /coded_by="NM_000375.1:197..994"
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                     [goid 0004852] [evidence IEA];
                     go_function: lyase activity [goid 0016829] [evidence IEA];
                     go_process: uroporphyrinogen III biosynthesis [goid
                     0006780] [evidence TAS] [pmid 2331520];
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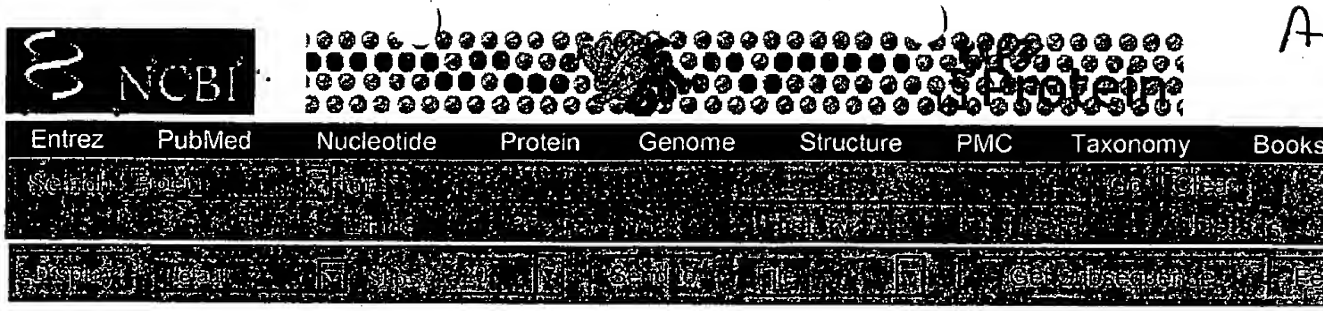

1: NP_000365. uroporphyrinogen ...[gi:9845522] BLink, Domains, Links

LOCUS NP_000365 367 aa linear PRI 21-DEC-2003
DEFINITION uroporphyrinogen decarboxylase; uroporphyrinogen III decarboxylase [Homo sapiens].
ACCESSION NP_000365
VERSION NP_000365.2 GI:9845522
DBSOURCE REFSEQ: accession NM_000374.2
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 367)
AUTHORS Wang,H., Long,Q., Marty,S.D., Sassa,S. and Lin,S.
TITLE A zebrafish model for hepatoerythropoietic porphyria
JOURNAL Nat. Genet. 20 (3), 239-243 (1998)
PUBMED 9806541
REFERENCE 2 (residues 1 to 367)
AUTHORS Mendez,M., Sorkin,L., Rossetti,M.V., Astrin,K.H., del C Batlle,A.M., Parera,V.E., Aizencang,G. and Desnick,R.J.
TITLE Familial porphyria cutanea tarda: characterization of seven novel uroporphyrinogen decarboxylase mutations and frequency of common hemochromatosis alleles
JOURNAL Am. J. Hum. Genet. 63 (5), 1363-1375 (1998)
PUBMED 9792863
REFERENCE 3 (residues 1 to 367)
AUTHORS Whitby,F.G., Phillips,J.D., Kushner,J.P. and Hill,C.P.
TITLE Crystal structure of human uroporphyrinogen decarboxylase
JOURNAL EMBO J. 17 (9), 2463-2471 (1998)
PUBMED 9564029
REFERENCE 4 (residues 1 to 367)
AUTHORS Moran-Jimenez,M.J., Ged,C., Romana,M., Enriquez De Salamanca,R., Taieb,A., Topi,G., D'Alessandro,L. and de Verneuil,H.
TITLE Uroporphyrinogen decarboxylase: complete human gene sequence and molecular study of three families with hepatoerythropoietic porphyria
JOURNAL Am. J. Hum. Genet. 58 (4), 712-721 (1996)
PUBMED 8644733
REFERENCE 5 (residues 1 to 367)
AUTHORS de Verneuil,H., Bourgeois,F., de Rooij,F., Siersema,P.D., Wilson,J.H., Grandchamp,B. and Nordmann,Y.
TITLE Characterization of a new mutation (R292G) and a deletion at the human uroporphyrinogen decarboxylase locus in two patients with hepatoerythropoietic porphyria
JOURNAL Hum. Genet. 89 (5), 548-552 (1992)
PUBMED 1634232
REFERENCE 6 (residues 1 to 367)
AUTHORS Romana,M., Grandchamp,B., Dubart,A., Amselem,S., Chabret,C., Nordmann,Y., Goossens,M. and Romeo,P.H.
TITLE Identification of a new mutation responsible for hepatoerythropoietic porphyria
JOURNAL Eur. J. Clin. Invest. 21 (2), 225-229 (1991)
PUBMED 1905636

REFERENCE 7 (residues 1 to 367)
AUTHORS Garey,J.R., Harrison,L.M., Franklin,K.F., Metcalf,K.M., Radisky,E.S. and Kushner,J.P.
TITLE Uroporphyrinogen decarboxylase: a splice site mutation causes the deletion of exon 6 in multiple families with porphyria cutanea tarda
JOURNAL J. Clin. Invest. 86 (5), 1416-1422 (1990)
PUBMED 2243121
REFERENCE 8 (residues 1 to 367)
AUTHORS Garey,J.R., Hansen,J.L., Harrison,L.M., Kennedy,J.B. and Kushner,J.P.
TITLE A point mutation in the coding region of uroporphyrinogen decarboxylase associated with familial porphyria cutanea tarda
JOURNAL Blood 73 (4), 892-895 (1989)
PUBMED 2920211
REFERENCE 9 (residues 1 to 367)
AUTHORS Romana,M., Dubart,A., Beaupain,D., Chabret,C., Goossens,M. and Romeo,P.H.
TITLE Structure of the gene for human uroporphyrinogen decarboxylase
JOURNAL Nucleic Acids Res. 15 (18), 7343-7356 (1987)
PUBMED 3658695
REFERENCE 10 (residues 1 to 367)
AUTHORS de Verneuil,H., Grandchamp,B., Beaumont,C., Picat,C. and Nordmann,Y.
TITLE Uroporphyrinogen decarboxylase structural mutant (Gly281----Glu) in a case of porphyria
JOURNAL Science 234 (4777), 732-734 (1986)
PUBMED 3775362
REFERENCE 11 (residues 1 to 367)
AUTHORS Dubart,A., Mattei,M.G., Raich,N., Beaupain,D., Romeo,P.H., Mattei,J.F. and Goossens,M.
TITLE Assignment of human uroporphyrinogen decarboxylase (URO-D) to the p34 band of chromosome 1
JOURNAL Hum. Genet. 73 (3), 277-279 (1986)
PUBMED 3460962
REFERENCE 12 (residues 1 to 367)
AUTHORS Romeo,P.H., Raich,N., Dubart,A., Beaupain,D., Pryor,M., Kushner,J., Cohen-Solal,M. and Goossens,M.
TITLE Molecular cloning and nucleotide sequence of a complete human uroporphyrinogen decarboxylase cDNA
JOURNAL J. Biol. Chem. 261 (21), 9825-9831 (1986)
PUBMED 3015909
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from U30787.1.
On Aug 18, 2000 this sequence version replaced gi:4507845.

Summary: This gene encodes the fifth enzyme of the heme biosynthetic pathway. This enzyme is responsible for catalyzing the conversion of uroporphyrinogen to coproporphyrinogen through the removal of four carboxymethyl side chains. Mutations and deficiency in this enzyme are known to cause familial porphyria cutanea tarda and hepatoerythropoetic porphyria.

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A-6

1: NP_000088. coproporphyrinoge...[gi:41393599] BLink, Links

LOCUS NP_000088 454 aa linear PRI 03-FEB-2004
DEFINITION coproporphyrinogen oxidase; coproporphyrinogen oxidase (coproporphyria, harderoporphyria) [Homo sapiens].
ACCESSION NP_000088
VERSION NP_000088.3 GI:41393599
DBSOURCE REFSEQ: accession NM_000097.4
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 454)
AUTHORS Colloc'h,N., Mornon,J.P. and Camadro,J.M.
TITLE Towards a new T-fold protein?: the coproporphyrinogen III oxidase sequence matches many structural features from urate oxidase
JOURNAL FEBS Lett. 526 (1-3), 5-10 (2002)
PUBMED 12208494
REMARK GeneRIF: coproporphyrinogen III oxidase sequence matches many structural features from urate oxidase
REFERENCE 2 (residues 1 to 454)
AUTHORS Wiman,A., Floderus,Y. and Harper,P.
TITLE Two novel mutations and coexistence of the 991C>T and the 1339C>T mutation on a single allele in the coproporphyrinogen oxidase gene in Swedish patients with hereditary coproporphyria
JOURNAL J. Hum. Genet. 47 (8), 407-412 (2002)
PUBMED 12181641
REMARK GeneRIF: disease-producing mutations in the CPO gene in nine Swedish families with hereditary coproporphyria
REFERENCE 3 (residues 1 to 454)
AUTHORS Rosipal,R., Lamoril,J., Puy,H., Da Silva,V., Gouya,L., De Rooij,F.W., Te Velde,K., Nordmann,Y., Martasek,P. and Deybach,J.C.
TITLE Systematic analysis of coproporphyrinogen oxidase gene defects in hereditary coproporphyria and mutation update
JOURNAL Hum. Mutat. 13 (1), 44-53 (1999)
PUBMED 9888388
REFERENCE 4 (residues 1 to 454)
AUTHORS Lamoril,J., Martasek,P., Deybach,J.C., Da Silva,V., Grandchamp,B. and Nordmann,Y.
TITLE A molecular defect in coproporphyrinogen oxidase gene causing harderoporphyria, a variant form of hereditary coproporphyria
JOURNAL Hum. Mol. Genet. 4 (2), 275-278 (1995)
PUBMED 7757079
REFERENCE 5 (residues 1 to 454)
AUTHORS Cacheux,V., Martasek,P., Fougerousse,F., Delfau,M.H., Druart,L., Tachdjian,G. and Grandchamp,B.
TITLE Localization of the human coproporphyrinogen oxidase gene to chromosome band 3q12
JOURNAL Hum. Genet. 94 (5), 557-559 (1994)
PUBMED 7959694
REFERENCE 6 (residues 1 to 454)
AUTHORS Delfau-Larue,M.H., Martasek,P. and Grandchamp,B.
TITLE Coproporphyrinogen oxidase: gene organization and description of a

mutation leading to exon 6 skipping
JOURNAL Hum. Mol. Genet. 3 (8), 1325-1330 (1994)
PUBMED 7987309
REFERENCE 7 (residues 1 to 454)
AUTHORS Martasek,P., Camadro,J.M., Delfau-Larue,M.H., Dumas,J.B., Montagne,J.J., de Verneuil,H., Labbe,P. and Grandchamp,B.
TITLE Molecular cloning, sequencing, and functional expression of a cDNA encoding human coproporphyrinogen oxidase
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 91 (8), 3024-3028 (1994)
PUBMED 8159699
REFERENCE 8 (residues 1 to 454)
AUTHORS Taketani,S., Kohno,H., Furukawa,T., Yoshinaga,T. and Tokunaga,R.
TITLE Molecular cloning, sequencing and expression of cDNA encoding human coproporphyrinogen oxidase
JOURNAL Biochim. Biophys. Acta 1183 (3), 547-549 (1994)
PUBMED 8286403
REFERENCE 9 (residues 1 to 454)
AUTHORS Kohno,H., Furukawa,T., Yoshinaga,T., Tokunaga,R. and Taketani,S.
TITLE Coproporphyrinogen oxidase. Purification, molecular cloning, and induction of mRNA during erythroid differentiation
JOURNAL J. Biol. Chem. 268 (28), 21359-21363 (1993)
PUBMED 8407975
COMMENT VALIDATED REFSEQ: This record has undergone preliminary review of the sequence, but has not yet been subject to final review. The reference sequence was derived from BC023551.2, BC023554.2, BC017210.2, Z28409.1 and BX648974.1.
On Jan 30, 2004 this sequence version replaced gi:20127406.
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A-7

1: NP_000300. protoporphyrinoge...[gi:4506001] BLink, Domains, Links

LOCUS NP_000300 477 aa linear PRI 15-MAR-2004
DEFINITION protoporphyrinogen oxidase [Homo sapiens].
ACCESSION NP_000300
VERSION NP_000300.1 GI:4506001
DBSOURCE REFSEQ: accession NM_000309.2
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
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REFERENCE 1 (residues 1 to 477)
AUTHORS Morgan,R.R., Errington,R. and Elder,G.H.
TITLE Identification of sequences required for the import of human protoporphyrinogen oxidase to mitochondria
JOURNAL Biochem. J. 377 (Pt 2), 281-287 (2004)
PUBMED 14535846
REMARK GeneRIF: Information required for targeting to the mitochondria is contained within the first 250 amino acid residues of human PPOX.
REFERENCE 2 (residues 1 to 477)
AUTHORS Maneli,M.H., Corrigall,A.V., Klump,H.H., Davids,L.M., Kirsch,R.E. and Meissner,P.N.
TITLE Kinetic and physical characterisation of recombinant wild-type and mutant human protoporphyrinogen oxidases
JOURNAL Biochim. Biophys. Acta 1650 (1-2), 10-21 (2003)
PUBMED 12922165
REFERENCE 3 (residues 1 to 477)
AUTHORS von und zu Fraunberg,M., Nyroen,T. and Kauppinen,R.
TITLE Mitochondrial targeting of normal and mutant protoporphyrinogen oxidase
JOURNAL J. Biol. Chem. 278 (15), 13376-13381 (2003)
PUBMED 12556518
REMARK GeneRIF: This enzyme in its regular and mutagenized forms is targeted to mitochondria when transfected.
REFERENCE 4 (residues 1 to 477)
AUTHORS Donnelly,J.G., Detombe,S. and Hindmarsh,J.T.
TITLE Single-strand conformational polymorphism and denaturing gradient gel electrophoresis in screening for variegate porphyria: identification of two new mutations
JOURNAL Ann. Clin. Lab. Sci. 32 (2), 107-113 (2002)
PUBMED 12017191
REMARK GeneRIF: Two previously undescribed mutations were identified: PPOX1423-1426-delATCT and PPOX2272insG.
REFERENCE 5 (residues 1 to 477)
AUTHORS Suzuki,Y., Ishihara,D., Sasaki,M., Nakagawa,H., Hata,H., Tsunoda,T., Watanabe,M., Komatsu,T., Ota,T., Isogai,T., Suyama,A. and Sugano,S.
TITLE Statistical analysis of the 5' untranslated region of human mRNA using 'Oligo-Capped' cDNA libraries
JOURNAL Genomics 64 (3), 286-297 (2000)
PUBMED 10756096
REFERENCE 6 (residues 1 to 477)
AUTHORS Whatley,S.D., Puy,H., Morgan,R.R., Robreau,A.M., Roberts,A.G.,

Nordmann,Y., Ellder,G.H. and Deybach,J.C.
TITLE Variegate porphyria in Western Europe: identification of PPOX gene mutations in 104 families, extent of allelic heterogeneity, and absence of correlation between phenotype and type of mutation
JOURNAL Am. J. Hum. Genet. 65 (4), 984-994 (1999)
PUBMED 10486317
REFERENCE 7 (residues 1 to 477)
AUTHORS Dailey,H.A. and Dailey,T.A.
TITLE Characteristics of human protoporphyrinogen oxidase in controls and variegate porphyrias
JOURNAL Cell. Mol. Biol. (Noisy-le-grand) 43 (1), 67-73 (1997)
PUBMED 9074790
REFERENCE 8 (residues 1 to 477)
AUTHORS Lam,H., Dragan,L., Tsou,H.C., Merk,H., Peacocke,M., Goerz,G., Sassa,S., Poh-Fitzpatrick,M., Bickers,D.R. and Christiano,A.M.
TITLE Molecular basis of variegate porphyria: a de novo insertion mutation in the protoporphyrinogen oxidase gene
JOURNAL Hum. Genet. 99 (1), 126-129 (1997)
PUBMED 9003509
REFERENCE 9 (residues 1 to 477)
AUTHORS Puy,H., Robreau,A.M., Rosipal,R., Nordmann,Y. and Deybach,J.C.
TITLE Protoporphyrinogen oxidase: complete genomic sequence and polymorphisms in the human gene
JOURNAL Biochem. Biophys. Res. Commun. 226 (1), 226-230 (1996)
PUBMED 8806618
REFERENCE 10 (residues 1 to 477)
AUTHORS Meissner,P.N., Dailey,T.A., Hift,R.J., Ziman,M., Corrigall,A.V., Roberts,A.G., Meissner,D.M., Kirsch,R.E. and Dailey,H.A.
TITLE A R59W mutation in human protoporphyrinogen oxidase results in decreased enzyme activity and is prevalent in South Africans with variegate porphyria
JOURNAL Nat. Genet. 13 (1), 95-97 (1996)
PUBMED 8673113
REFERENCE 11 (residues 1 to 477)
AUTHORS Dailey,T.A. and Dailey,H.A.
TITLE Human protoporphyrinogen oxidase: expression, purification, and characterization of the cloned enzyme
JOURNAL Protein Sci. 5 (1), 98-105 (1996)
PUBMED 8771201
REFERENCE 12 (residues 1 to 477)
AUTHORS Dailey,T.A., Dailey,H.A., Meissner,P. and Prasad,A.R.
TITLE Cloning, sequence, and expression of mouse protoporphyrinogen oxidase
JOURNAL Arch. Biochem. Biophys. 324 (2), 379-384 (1995)
PUBMED 8554330
REFERENCE 13 (residues 1 to 477)
AUTHORS Taketani,S., Inazawa,J., Abe,T., Furukawa,T., Kohno,H., Tokunaga,R., Nishimura,K. and Inokuchi,H.
TITLE The human protoporphyrinogen oxidase gene (PPOX): organization and location to chromosome 1
JOURNAL Genomics 29 (3), 698-703 (1995)
PUBMED 8575762
REFERENCE 14 (residues 1 to 477)
AUTHORS Nishimura,K., Taketani,S. and Inokuchi,H.
TITLE Cloning of a human cDNA for protoporphyrinogen oxidase by complementation in vivo of a hemG mutant of Escherichia coli
JOURNAL J. Biol. Chem. 270 (14), 8076-8080 (1995)
PUBMED 7713909
REFERENCE 15 (residues 1 to 477)
AUTHORS Dailey,T.A., Meissner,P. and Dailey,H.A.
TITLE Expression of a cloned protoporphyrinogen oxidase
JOURNAL J. Biol. Chem. 269 (2), 813-815 (1994)
PUBMED 8288631
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from AU076582.1, AI357309.1 and

BC002357.2.

Summary: This gene encodes the penultimate enzyme of heme biosynthesis, which catalyzes the 6-electron oxidation of protoporphyrinogen IX to form protoporphyrin IX. This protein is a flavoprotein associated with the outer surface of the inner mitochondrial membrane. Mutations in this gene cause variegate porphyria.

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1: NP_000131. ferrochelatase [H...[gi:4557593] BLink, Domains, Links

LOCUS NP_000131 423 aa linear PRI 20-DEC-2003
DEFINITION ferrochelatase [Homo sapiens].
ACCESSION NP_000131
VERSION NP_000131.1 GI:4557593
DBSOURCE REFSEQ: accession NM_000140.1
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 423)
AUTHORS Minder,E.I., Gouya,L., Schneider-Yin,X. and Deybach,J.C.
TITLE A genotype-phenotype correlation between null-allele mutations in the ferrochelatase gene and liver complication in patients with erythropoietic protoporphyria
JOURNAL Cell. Mol. Biol. (Noisy-le-grand) 48 (1), 91-96 (2002)
PUBMED 11929053
REMARK GeneRIF: Data indicate a significant genotype-phenotype correlation between 'null allele' mutation and protoporphyrin related liver disease in erythropoietic protoporphyria.
REFERENCE 2 (residues 1 to 423)
AUTHORS Chen,F.P., Risheg,H., Liu,Y. and Bloomer,J.
TITLE Ferrochelatase gene mutations in erythropoietic protoporphyria: focus on liver disease
JOURNAL Cell. Mol. Biol. (Noisy-le-grand) 48 (1), 83-89 (2002)
PUBMED 11929052
REMARK GeneRIF: Mutations in the FECH gene could not account the development of liver disease in the severe phenotype of erythropoietic protoporphyria(EPP).
REFERENCE 3 (residues 1 to 423)
AUTHORS Tugores,A., Magness,S.T. and Brenner,D.A.
TITLE A single promoter directs both housekeeping and erythroid preferential expression of the human ferrochelatase gene
JOURNAL J. Biol. Chem. 269 (49), 30789-30797 (1994)
PUBMED 7983009
REFERENCE 4 (residues 1 to 423)
AUTHORS Brenner,D.A., Didier,J.M., Frasier,F., Christensen,S.R., Evans,G.A. and Dailey,H.A.
TITLE A molecular defect in human protoporphyria
JOURNAL Am. J. Hum. Genet. 50 (6), 1203-1210 (1992)
PUBMED 1376018
REFERENCE 5 (residues 1 to 423)
AUTHORS Nakahashi,Y., Fujita,H., Taketani,S., Ishida,N., Kappas,A. and Sassa,S.
TITLE The molecular defect of ferrochelatase in a patient with erythropoietic protoporphyria
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 89 (1), 281-285 (1992)
PUBMED 1729699
REFERENCE 6 (residues 1 to 423)
AUTHORS Diep,A., Li,C., Klisak,I., Mohandas,T., Sparkes,R.S., Gaynor,R. and Lusis,A.J.
TITLE Assignment of the gene for cyclic AMP-response element binding

protein 2 (CREB2) to human chromosome 2q24.1-q32
JOURNAL Genomics 11 (4), 1161-1163 (1991)
PUBMED 1838349
REFERENCE 7 (residues 1 to 423)
AUTHORS Nakahashi,Y., Taketani,S., Okuda,M., Inoue,K. and Tokunaga,R.
TITLE Molecular cloning and sequence analysis of cDNA encoding human ferrochelatase
JOURNAL Biochem. Biophys. Res. Commun. 173 (2), 748-755 (1990)
PUBMED 2260980
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from D00726.1.

Summary: Ferrochelatase is localized to the mitochondrion where it catalyzes the insertion of ferrous form of iron into protoporphyrin IX in the heme synthesis pathway. Defects in ferrochelatase are associated with protoporphyria.

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go_function: lyase activity [goid 0016829] [evidence IEA];
go_function: magnesium chelatase activity [goid 0016851] [evidence IEA];
go_function: cobalt chelatase activity [goid 0016852] [evidence IEA];
go_process: heme biosynthesis [goid 0006783] [evidence

TAS] [pmid 1729699];
go_process: response to light [goid 0009416] [evidence TAS] [pmid 1376018];
go_process: energy pathways [goid 0006091] [evidence TAS] [pmid 1729699]"
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ORIGIN

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